Clinical Trial Notes

Phase II Trial of Concurrent Chemoradiotherapy with S-1 Plus Cisplatin in Patients with Unresectable Locally Advanced Squamous Cell Carcinoma of the Head and Neck: Japan Clinical Oncology Group Study (JCOG0706)

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Received March 19, 2009; accepted April 1, 2009; published online May 8, 2009

A Phase II study was started in Japan to evaluate the efficacy and safety of concurrent chemoradiotherapy with S-1 plus cisplatin in patients with unresectable locally advanced squamous cell carcinoma of the head and neck. This study began in July 2008, and a total of 45 patients will be accrued from 13 institutions within 2 years. The primary endpoint is the clinical complete remission rate. The secondary endpoints are local progression-free survival, overall survival, progression-free survival, time to treatment failure, proportion of patients who achieve nutritional support-free survival and adverse events.

Key words: head and neck neoplasms – chemoradiotherapy – clinical trials – Phase II

INTRODUCTION

More than 60% of squamous cell carcinomas of the head and neck (SCCHN) are revealed to be Stage III or IV at diagnosis, because they are not symptomatic and it is difficult to detect them in their early stages (1). The prognosis of unresectable locally advanced SCCHN is still poor.

The standard therapy for locally advanced SCCHN is chemoradiotherapy (CRT) with cisplatin alone or 5-fluorouracil (5-FU) plus cisplatin (2–5). S-1 is a new oral fluoropyrimidine, consisting of tegafur, 5-chloro-2,4-dihydroxypyrimidine and potassium oxonate, which as monotherapy led to a response rate of 34.1% in patients with progressive or recurrent SCCHN (6). S-1 monotherapy also demonstrated a response rate of 30.4% in patients with pre-treated SCCHN, which was much better than the response rate of 15% seen with 5-FU continuous infusion (6). Thus, higher efficacy may be expected if 5-FU is replaced with S-1 in CRT as well as in chemotherapy alone. A Phase I study of concurrent CRT with S-1 plus CDDP in patients with unresectable locally advanced SCCHN showed quite a high complete response rate (86%) (7). Therefore, we have undertaken a Phase II study to evaluate the efficacy and safety of concurrent CRT with S-1 plus CDDP for patients with unresectable locally advanced SCCHN. The Protocol Review Committee of the Japan Clinical Oncology Group (JCOG) approved the protocol in June 2008 and the study was activated in July 2008. This trial was registered at the UMIN Clinical Trials Registry as UMIN000001272 (http://www.umin.ac.jp/ctr/index.htm).

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PURPOSE
The aim of this study is to evaluate the efficacy and safety of concurrent CRT with S-1 plus cisplatin in patients with unresectable locally advanced SCCHN.

STUDY SETTING
The study is a multi-institutional Phase II study.

RESOURCES
The study is supported by Grants-in-Aid for Cancer Research (18-19, 20S-3, 20S-6) from the Ministry of Health, Labour and Welfare of Japan.

ENDPOINTS

The primary endpoint is the clinical complete remission rate, which is the proportion of complete response (CR) and good partial response (good PR) in all eligible patients. Good PR is defined as a remaining secondary change with tumor shrinkage such that the remaining tissue is not regarded as residual tumor but rather as scar material. Our evaluative guidelines suggested identifying good PR lesions as ~10 mm or less in size and not enhanced on contrasted computed tomography scan. The secondary endpoints are local progression-free survival, progression-free survival, overall survival, time to treatment failure, proportion of patients achieving nutritional support-free survival and adverse events.

Local progression-free survival is the time from enrollment to local disease progression or death from any cause. Progression-free survival is defined as the time from enrollment to any disease progression or death from any cause. Overall survival is defined as days from enrollment to death from any cause. Time to treatment failure is defined as the time from enrollment to any disease progression, off-protocol treatment or death from any cause. Proportion of nutritional support-free survival denotes the percentage of surviving patients not requiring any nutritional support at the time of treatment start and then 2, 6, 12 and 24 months after registration.

ELIGIBILITY CRITERIA

INCLUSION CRITERIA
For inclusion in the study, the patient must fulfill all of the following criteria: (i) histologically proven squamous cell carcinoma; (ii) primary lesion located at oropharynx, hypopharynx or larynx; (iii) unresectable locally advanced head and neck cancer which fulfills at least one of the following conditions: (a) primary lesion or cervical lymph node metastasis to carotid artery, cranial base or cervical vertebrae; (b) cervical lymph node metastasis of N2c or N3 (UICC/TNM, 6th edition); and (c) T4 primary lesion located at oropharynx; (iv) no fistula due to primary lesion or cervical lymph node metastasis; (v) no distant metastasis; (vi) age between 20 and 75 years old; (vii) ECOG performance status of 0 or 1; (viii) no prior radical surgery for head and neck cancer; (ix) no prior treatment for any other malignancies with chemotherapy, radiation therapy or endocrine therapy; (x) sufficient organ function; (xi) normal electrocardiogram; and (xii) written informed consent.

EXCLUSION CRITERIA

Patients are excluded if they meet any of the following criteria: (i) active bacterial or fungous infection; (ii) simultaneous or metachronous (within 5 years) double cancers except carcinoma in situ or intramucosal tumor; (iii) women during pregnancy or breastfeeding; (iv) active gastrointestinal bleeding; (v) pleural effusion, pericardial effusion or massive ascites; (vi) history of severe heart disease, heart failure, myocardial infarction within 6 months or angina pectoris attack within 6 months; (vii) cerebrovascular disease within 6 months; (viii) diabetes mellitus treated with insulin or poorly controlled; (ix) poorly controlled hypertension; (x) chronic pancreatitis; (xi) positive HBs antigen; (xii) impossibility to refrain from smoking and drinking during treatment; and (xiii) requiring systemic steroids medication.

TREATMENT METHODS

The protocol treatment consists of concurrent CRT, adjuvant chemotherapy and salvage surgery if necessary (Fig. 1).

First, patients receive concurrent CRT with S-1 plus cisplatin. S-1 (60 mg/m²/day) is orally administered for two weeks and cisplatin is infused on days 8 through 11, repeated every five weeks for two courses.

Radiation therapy is administered with high-energy photons of 4–10 MV X-rays to a total dose of 70 Gy in a fraction of 2 Gy five times weekly. The gross tumor volume (GTV) includes the volumes of both the primary tumor and metastatic cervical lymph nodes with a short axis of 1 cm or larger. The clinical target volume 1 (CTV1) includes GTV and bilateral regional cervical lymph node area with a 1–2 cm margin, and CTV2 includes GTV with a 0.5–2 cm margin. The planning target volumes (PTVs) for CTV1 and CTV2 (PTV1 and PTV2) are defined as 0.5–1 cm margins around CTV to compensate for set-up variations and internal organ motion. A total of 40 Gy is delivered toward PTV1, and then an additional 30 Gy is boosted to PTV2.

For patients with an objective response (CR, good PR or PR) at the first evaluation after CRT, adjuvant chemotherapy with S-1 plus cisplatin is administered for two more courses. In adjuvant chemotherapy, S-1 (60 mg/m²/day) is orally administered for two courses and cisplatin (20 mg/m²/day) is infused on days 8 through 11, repeated every four weeks. At the second evaluation after adjuvant chemotherapy, patients diagnosed with CR or good PR are regarded as having completed the protocol treatment. Patients not diagnosed with CR or...
good PR are discontinued from treatment, and salvage surgery is planned if it is judged to be clinically feasible.

**FOLLOW-UP**

All enrolled patients are followed up for at least 3 years. Efficacy and safety are to be evaluated at least every 3 months during the first year, at least every 4 months during the second year and then every 6 months during the third year. Data on the use and methodology of nutritional support are reported at 2, 6, 12 and 24 months after registration.

**STUDY DESIGN AND STATISTICAL ANALYSIS**

This trial is designed to evaluate the efficacy and safety of CRT with S-1 plus cisplatin and to determine the viability of proceeding to a Phase III trial. In this Phase II trial, the planned sample size is 45 patients, which was calculated by SWOG’s (Southwest Oncology Group) two-stage attained design (8) based on an expected clinical complete remission rate of 60% and a threshold of 45%, with a one-sided \( \alpha \) error of 0.1 and a \( \beta \) error of 0.1. If at least 10 clinical complete remissions occur after the first 25 patients enroll, another 20 patients will be accrued.

If the clinical complete remission rate is as high as expected, the subsequent Phase III trial will be designed to confirm the superiority of CRT with S-1 plus cisplatin to CRT with cisplatin alone.

**INTERIM ANALYSIS AND MONITORING**

In this Phase II trial, an interim analysis is planned once, which corresponds to the first-stage analysis in the two-stage design. The Data and Safety Monitoring Committee (DSMC) of the JCOG will independently review the interim analysis reports and recommend that the trial either be continued or terminated early. Central monitoring will be performed every 6 months by the Data Center to evaluate and improve study progress and quality.

**PARTICIPATING INSTITUTIONS (FROM NORTH TO SOUTH)**

Hokkaido University Hospital, Miyagi Cancer Center, Yamagata Prefectural Central Hospital, Jichi Medical University Hospital, National Cancer Center Hospital East, Tokyo Women’s Medical University Hospital, National Hospital Organization Tokyo Medical Center, Kanagawa Cancer Center, Shizuoka Cancer Center, Aichi Cancer Center, Kobe University Hospital, Hyogo Cancer Center and Shikoku Cancer Center.

**Funding**

This work is supported by Grant-in-Aid for Cancer Research (18-19, 20S-3, 20S-6) from the Ministry of Health, Labour and Welfare of Japan.

**Conflict of interest statement**

None declared.

**References**


